REMARKS

Claims 1-17 are pending in the above-identified application. Support for new claim 17 is found at page 4, lines 33-37, for example.

Expected Submission of Additional Evidence

Applicant has requested a three-month suspension in prosecution and intends to submit additional evidence in support of the patentability of the present claims in the near future. It is requested that the Examiner await receipt of this evidence and fully consider it upon submission.

Final Office Action of September 3, 2009

The Patent Examiner issued a Final Office Action on September 3, 2009 in which he maintained his position in rejecting the presently considered claims over the combinations of : [1] GlaxoSmithKline ("Prescribing Information; Navelbine (vinorelbine tartrate) Injection", 2002, Nov., pp. 1-17) and Duflos '377 (US 6,127,377); [2] Wolgemuth '643 (CA 2,001,643) and Duflos '377; and [3] GlaxoSmithKline, Duflos '377, Wolgemuth '643, and further in view of Howell ("Anti-vascular effects of vinflunine...," British Journal of Cancer (2001) **84** (2), pp. 290-295.)

It is essentially the position of the Examiner that Duflos '377 generally discloses the family of vinblastine and vinorelbine compounds including vinflunine, and that the disclosure in GlaxoSmithKline of vinorelbine tartrate in an aqueous solution without preservatives, as well as the disclosure in Wolgemuth '643 of injectionable aqueous solutions of vincristine that include preservatives such as mannitol, suggests to one skilled in the art that the claimed vinflunine ditartrate salt may be stable in an aqueous solution without preservatives.

Applicant submitted evidence into the record including the Declaration under 37 CFR 1.132 by Elie Leverd (the Leverd Declaration) which establishes that the physico-chemical properties between vinflunine and the related vinorelbine tartrate compounds differ significantly such that one skilled in the art would not expect both of these compounds to be stable in an aqueous solution without preservatives. However, the Examiner has offered several criticisms of

the evidence stating that, "There is no evidence of record ...[of] any correlation between solubility and stability," (page 5, lines 5-7 of Final Office Action). That is, the Examiner has refused to accept the premise that the differences in physico-chemical properties between vinflunine and vinorelbine would suggest to one skilled in the art that these compounds would have different solubility and stability properties when in solution. In view of this stated position, Applicant intends to submit additional evidence addressing these issues. It is also submitted that the present patent claims define over the previously cited references based on the following reasons.

Present Invention

The present invention is directed to a vinflunine pharmaceutical composition in the form of a stable and sterile aqueous solution of a water-soluble vinflunine salt at a pH between 3 and 4, which does not contain any sugar, sugar-based polyol or other preservatives, as recited in claim 1. As explained at pages 1-4 of the present specification, conventional pharmaceutical formulations containing vinflunine did not exhibit acceptable storage stability properties or required somewhat complex methods for preparing injectable formulations. However, the composition of the present invention overcomes these problems and exhibits advantageously improved storage stability properties without requiring complicated techniques or the presence of multiple preservatives. The improved stability properties exhibited by the composition of the present invention are evidenced by the test results described in connection with Examples 1 and 2 at pages 8-13 of the present specification.

Distinctions over Previously Cited References

GlaxoSmithKline and Duflos '377 References

GlaxoSmithKline discloses a composition for intravenous administration which includes vinorelbine tartrate equivalent to 10 or 15 mg in water with no preservatives, wherein the aqueous solution is sterile and nonpyroginic. The pH of the composition is approximately 3.5.

Duflos '377 discloses vinca alkaloid antimitotic halogenated derivates of the vinblastine and vinorelbine family, including vinflunine as disclosed in the abstract thereof. Duflos '377 discloses vinflunine ditartrate at col. 13, lines 39-42.

Both GlaxoSmithKline and Duflos '377 fail to disclose or suggest the composition of the present invention containing a stable and sterile aqueous solution of a water-soluble vinflunine salt at a pH between 3 and 4, which does not contain any sugar, sugar-based polyol or other preservatives. GlaxoSmithKline only relates to vinorelbine containing formulations. Duflos '377 mentions vinflunine, but fails to disclose any suggestion about formulating a vinflunine salt in an aqueous solution without preservatives as in the composition of the present invention. Duflos '377 also fails to suggest substituting vinflunine for vinorelbine in aqueous solutions with the expectation that similar stability properties would be exhibited.

It has been alleged by the Examiner that it would have been obvious for one skilled in the art to substitute the vinorelbine ditartrate described in GlaxoSmithKline with vinflunine ditartrate disclosed in Duflos '377 in order to arrive at the presently claimed invention. However, such a suggested substitution is not disclosed in GlaxoSmithKline or Duflos '377 and would not have been predictable in view of the significant differences in properties between vinorelbine and vinflunine. In fact, vinorelbine and vinflunine, even if they may have similar therapeutic properties, exhibit totally different physico-chemical properties in the form of a powder or in form of an aqueous solution. First, there are differences in water solubility: vinorelbine tartrate has a solubility higher than 1000 mg/ml whereas vinflunine tartrate has a solubility equal to only 290 mg/ml. Second, there are significantly different properties exhibited by each in the form of a powder after 6 months of storage at 5°C: vinorelbine tartrate degrades such that the major impurity is due to the oxidation of the alcohol group in the vindoline structure, whereas in contrast, vinflunine ditartrate degrades such that the major impurity is 23-0 dimethylvinflunine which is due to the hydrolysis of the ester group of the vindoline structure. Therefore, vinorelbine tartrate and vinflunine ditartrate generate very different major impurities. Third, the process for manufacturing vinflunine is totally different from the process for manufacturing vinorelbine. It is a more complex process since it requires a super acid medium. Fourth, vinorelbine exhibits fungicidal activity after up to 28 days of contact with mold spores,

with a slight fungicidal activity after 24 hours of contact. In contrast, vinflunine exhibits no fungicidal activity. Consequently, several significant properties differ between these two compounds, such that one skilled in the art would not conclude it would be predictable to employ one compound in place of another and expect the same physico-chemical properties to be exhibited together with any improved storage stability properties. Vinflunine seems to be less stable than vinorelbine since it has a lower solubility. Vinflunine degrades to form a major impurity significantly different from vinorelbine and does not exhibit fungicidal activity as does vinorelbine. Therefore, the behavior of vinflunine in an aqueous solution can not be predicted based on the different physico-chemical properties exhibited by vinorelbine.

The Examiner has previously referred to MPEP 2144.06.II and stated that vinflunine and vincristine have the same art-recognized equivalent activities. However, Applicant respectfully submits that reference to MPEP 2144.06.II is inappropriate in this context. MPEP 2144.06.II states that, "In order to rely on equivalence as a rationale supporting an obviousness rejection, the equivalency must be recognized in the prior art, and cannot be based on applicant's disclosure or the mere fact that the components at issue are functional or mechanical equivalents. In re Ruff, 256 F.2d 590, 118 USPQ 340 (CCPA 1958)". Duflos '377 discloses that dimeric alkaloids of C. roseus and their derivatives commonly referred as vinea alkaloids, have been widely used in anticancer chemotherapy for about 30 years. They are presented by four products: vinblastine, vincristine, vindesine and vinorelbine (column 1, line 9 to column 2 line 15). Vinflunine is not mentioned. Moreover, there is nothing in either of the two documents mentioning that "vinca alkaloids" can be considered "equivalents" when speaking about solution for injection. In fact, the above-noted inconsistencies among the physico-chemical properties of these four products, as further evidenced by the previously submitted Leverd Declaration under 37 CFR 1.132 establish that there is no accepted equivalency as alleged by the Examiner.

Consequently, significant patentable distinctions exist between the present invention and both of the GlaxoSmithKline and Duflos '377 references, whether taken separately or hypothetically combined. Further, even if these references were hypothetically combined, there fails to be any recognition of the advantageously improved storage stability properties evidenced by the comparative experimental tests described in Examples 1 and 2 of the present specification

which rebuts any allegation of *prima facie* obviousness based on this combination. Therefore, it is requested that the rejections based on these references not be maintained.

Wolgemuth '643 Reference

Wolgemuth '643 is discussed at page 3, lines 26-32 of the present specification. Wolgemuth '643 relates to an injectable solution of vincristine, and discloses the use of an acetic acid/sodium acetate buffer to maintain a pH of the solution of between 3.5 and 5.5, preferably between 4.0 and 4.5. Wolgemuth '643 discloses at page 4, line 30 to page 5, line 3 that the described compositions may contain excipients, including sugars or polyols derived from sugars, such as mannitol. As described in Example 1 at pages 6-7 of the Wolgemuth '643, all the composition examples require mannitol. Although, Wolgemuth '643 may be interpreted to imply that the compositions therein do not require a sugar or sugar-based polyol, there fail to be any operative examples without such a component.

Wolgemuth '643 fails to disclose a composition which includes vinflunine. Wolgemuth '643 fails to disclose any examples which do not at least include a sugar-based polyol which is excluded from the composition of the present invention as recited in the present claims. Consequently, one skilled in the art would not find a disclosure or suggestion in Wolgemuth '643 to form compositions that do not at least contain a sugar-based polyol. Further, there fails to be any suggestion in Wolgemuth '643 to substitute vinflunine for vincristine.

In addition, it is submitted that Wolgemuth '643 indicates that the vincristine solution may contain minor amounts of sugars and agents to buffer the pH which means that the excipients are not incompatible with the formulation. Indeed the recitation in the claims that the formulation "[consists] essentially of" leaves the door open to other excipients rather than an absence of any excipients at all. The amount of degradation products in the tested samples of the solution of Example I in Table 5 which contains mannitol grows from 2.4 % to 3.5 %, which constitutes an increase of 25 to 46% of the amount of impurities over 7 days. Therefore, this solution is less stable than the solution according to the present invention while containing mannitol. The product also loses activity by 3% over 7 days only. Therefore, one skilled in the art would have thought that removing mannitol would have a strong impact on the stability of the solution and would not

have considered this option. This is confirmed by the fact that the vincristine sulphate parenteral formulation is commercialized under the tradename ONCOVIN® which according to a published Label (dated July 1999) contains mannitol. Thus, it is unreasonable to conclude that a person skilled in the art would have selected the option of not adding mannitol to a formulation of vinflunine in view of the stability results presented for the solution of Example I Wolgemuth '643 in view of the commercialized product ONCOVIN®. Consequently, significant patentable distinctions exist between the present invention and Wolgemuth '643 such that the rejections based on this reference should not be maintained.

Howell et al. Reference

According to the Examiner, it would have been obvious in view of Howell et al. to increase the quantity of vinflunine as was been done for vinorelbine or vincristine in order to optimize the quantity and to obtain the claimed concentration claimed. First, it is submitted that Howell et al. fails to disclose or suggest the aqueous vinflunine composition of the present invention and fails to make up for any of the deficiencies noted above with regard to the other cited references. Secondly, as indicated above, vinflunine has a lower solubility than vinorelbine. Vinorelbine is used at a concentration of 10 mg/ml. As a consequence, it was not predictable that a stable aqueous solution of vinflunine having a concentration of between 25 and 30 mg/ml could be obtained, since an aqueous solution at 70 mg/ml precipitates after 2 months of storage at 5°C±3°C. Howell et al. fails to address this issue. Consequently, significant patentable distinctions exist between Howell et al. and the present invention, whether taken alone or hypothetically combined with the other cited references, such that the rejections based on this reference should be withdrawn.

If any questions arise in the above matters, please contact Applicant's representative, Andrew D. Meikle (Reg. No. 32,868), in the Washington Metropolitan Area at the phone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37.C.F.R. §§1.16 or 1.17; particularly, extension of time fees.

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Respectfully submitted,

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